In the Specification:

On page 40, please replace the paragraph beginning at line 1 with the following:

-- N-terminal hydrophobic residues from the TM5 helix were then replaced with a palmitate lipid ($C_{16}H_{31}O$) to drastically reduce the size of the i3 peptides. Palmitoylated peptides were synthesized by standard fmoc solid phase synthetic methods with C-terminal amides. Palmitic acid was dissolved in 50% N-methyl pyrolidone/50% methylene chloride and coupled overnight to the deprotected N-terminal amine of the peptide. After cleavage from the resin, palmitoylated peptides were purified to >95% purity by C18 or C4 reverse phase chromatography. As shown in FIG. 1B, the palmitoylated i3 loop peptide, P1pal-19 causes a rapid Ca2+i transient that is identical in profile to that caused by the extracellular PAR1 ligand, SFLLRN (SEQ ID NO:24). B1 In addition, P1pal-19 fully activates platelet aggregation (FIG. 1D) with an EC50 of 8 ± 3 micromolar. Individual aggregation traces of platelets stimulated with 10 Micromolar of indicated peptides or palmitic acid and platelet aggregation was monitored as % light transmittance of stirred platelets at 37 °C as described (L. Covic, A. L. Gresser, A. Kuliopulos, *Biochemistry* 39, 5458-5467 (2000).). P1pal-19 completely inhibits the subsequent Ca2+i response to 30 micromolar SFLLRN (SEQ ID NO:24) (FIG. 1C) due to desensitization of PAR1. Similarly, prestimulation with SFLLRN (SEQ ID NO:24) completely desensitizes the platelets to P1pal-19. Palmitic acid by itself has no effect on Ca 2+i and platelet aggregation (FIG. 1B, D).--

On page 42, please replace the paragraph beginning at line 25 with the following:

-- PAR1-Rat1 cells or PAR2-COS7 cells were challenged with 1 nM to 10-100 ?M i3 peptide or mastoparan (INLKALAALAKKIL) (SEQ ID NO:25). PLC-beta activity was determined by measuring total [3H]-inositol phosphate (InsP) formation. As shown in FIG. 2B and C, P1pal-19, and P1pal-13 which lacks the N-terminal six residues of P1pal-19, stimulate InsP production with EC50 values of 180 ± 20 nM and 700 ± 50 nM, respectively, and with similar efficacies as the natural agonist thrombin. In B and C, PLC-? activity was converted to percent of the full response relative to 0.1 nM thrombin (100%) and plotted as a function of peptide B2 concentration using a two-site equation that fit the biphasic activation and inhibition profiles. The full PAR1 thrombin responses for individual experiments were 7.6-fold for P1pal-13, 9.4-fold for P1pal-12 and P1pal-7, 12.4-fold for P1pal-19 and P1pal-19/Rat1 alone, 18-fold for P1pal-19Q, 12.4-fold for P1pal-19E and 9.5-fold for the mastoparan experiment. The minor stimulation of untransfected Rat1 cells (Rat1 alone) by P1pal-19 in C can be attributed to the endogenous rat PAR1 present in these fibroblasts since addition of SFLLRN (SEQ ID NO:24) causes similar stimulation in these untransfected cells (FIG. 2F-'RAT1').--

On page 43, please replace the paragraph beginning at line 12 with the following:

-- The activation curves of PAR1 are biphasic with a steep activating phase followed by a steep inhibitory phase. Splitting the P1pal-19 agonist into C-terminal P1pal-7 and corresponding N-terminal P1pal-12 peptides results in loss of stimulatory activity in platelets or PAR1-Rat1 cells when added separately (FIGS. 1B, 1D, 2B) or together (FIG. 1B). Therefore, in order to have agonist activity, C-terminal PAR1 pepducin residues 301-313 must be contiguous. COS7 cells were transiently transfected with the human receptors PAR1, PAR2, PAR4, cholecystokinin A (CCKA), cholecystokinin B (CCKB), substance P (Sub-P), or rat somatostatin receptor (SSTR2). Transfected cells were challenged with a range of concentrations (0.1-10 micromolar) of P1pal-19, P1pal-13, or P2pal-21 and the highest stimulation of the individual receptors is reported as a black column. The extracellular agonists used to define maximum stimulation for each receptor (open column) were 10 nM thrombin for PAR1, 100 micromolar SLIGKV (SEQ ID NO:17) for PAR2, 100 nM thrombin for PAR4, 300 nM CCK-8 for CCKA and CCKB, 1 micromolar AGCKNFFWKTFTSC (SEQ ID NO:18) for SSTR2, and 1.5 micromolar RPKPQQFFGLM (SEQ ID NO:26) for Sub-P. The full activity profiles for P1pal-19 and P1pal-13 against these receptors are included as supplementary material (Supplementary information is available on *Science* Online at www.sciencemag.org).--

On page 46, please replace the paragraph beginning at line 20 with the following:

-- Next, to help distinguish between indirect versus direct activation of the G protein by the pepducins, a point mutation was introduced at position S309 located in the C-terminus of the i3 loop/N-terminus of TM6 of PAR1. This perimembranous region has been shown to be important for the fidelity of G protein coupling for many receptorsS. Cotecchia, J. Ostrowski, M. A. Kjelsberg, M. G. Caron, R. J. Lefkowitz, *J. Biol. Chem.* 267, 1633-1639 (1992). ()E. Kostenis, B. R. Conklin, J. Wess, *Biochemistry* 36, 1487-1495 (1997); M. A. Kjelsberg, S. Cotecchia, J. Ostrowski, M. G. Caron, R. J. Lefkowitz, *J. Biol. Chem.* 267, 1430-1433 (1992). and comes into direct contact with the critical DRY residues of TM3 ()K. Palczewski *et al.*, *Science* 289, 739-45 (2000). A S309P mutant was constructed and transiently expressed in COS7 cells to the same level as wild type PAR1. COS7 cells were transiently transfected with wild-type (WT), S309P or delta377 PAR1 (A. Kuliopulos *et al.*, *Biochemistry* 38, 4572-4585 (1999) receptors. Cells were challenged with P1pal-19, SFLLRN (SEQ ID NO:24), or thrombin and PLC-beta activity determined by measuring total [3H]-inositol phosphate formation relative to 100% stimulation (9.6-fold) of WT PAR1 with 0.1 nM thrombin. The apparent inhibition of PAR1 by very high concentrations of thrombin in B is caused by persistent interactions of thrombin to a hirudin-like sequence (K51YEPF55) located in the e1 exodomain of PAR1 (D. T. Hung, T.-K. H. Vu, V. I. Wheaton, K. Ishii, S. R. Coughlin, *J. Clin. Invest.* 89, 1350-1353 (1992)). High amounts of thrombin can remain bound to the thrombin-cleaved PAR1 exodomain (S. L. Jacques, M. LeMasurier, P. J. Sheridan, S. K. Seeley, A. Kuliopulos, *J. Biol. Chem.* 275, 40671-40678 (2000)) and inhibit intramolecular liganding by the tethered SFLLRN (SEQ ID NO:24).--

On page 47, please replace the paragraph beginning at line 15 with the following:

-- The S309P mutant is deficient in thrombin- and SFLLRN-dependent (SEQ ID NO:24) stimulation of InsP with 17- and 28-fold loss of potency, and 1.6- and 3.3-fold loss of efficacy, respectively (FIG. 3B, C). Interestingly, P1pal-19 also stimulates the S309P mutant with parallel losses in potency (13-fold) and efficacy (4.3-fold) relative to its effects on wild type PAR1 (FIG. 3A). Since P1pal-19 did not correct the signaling defect of the S309P mutation, this indicates that the crucial C-terminal portion of the i3 region in the intact receptor exerts dominant effects in coupling to G protein over that of the exogenous pepducin.--

B5

On page 48, please replace the paragraph beginning at line 2 with the following:

-- To define the region(s) of the receptor that might directly contact the i3-pepducin, the entire C-terminal i4 domain of PAR1 was deleted (delta377). The X-ray structure of rhodopsin (K. Palczewski *et al.*, *Science* 289, 739-45 (2000)) indicates that the i3 loop may contact the N-terminal region of alpha-helix 8 and residues to the C-terminal side of the Cys-palmitate moieties within the i4 C-tail. As shown in FIG. 3B and C, the delta377 mutant is defective in stimulating PLC-beta in response to thrombin and SFLLRN (SEQ ID NO:24). Efficacy is reduced by 2-3 fold for the two PAR1 agonists and potency is shifted 22-fold for thrombin and ~30-fold for SFLLRN (SEQ ID NO:24). In contrast, the P1pal-19 pepducin gives effectively no stimulation of PLC-beta in the presence of the delta377 PAR1 mutant (FIG. 3A). These data demonstrate that the C-tail of PAR1 is required for P1pal-19 to activate G-protein and that the C-tail may provide a binding surface for the pepducin agonists.--

B6

On page 49, please replace the paragraph beginning at line 2 with the following:

-- Human platelets were a convenient, biologically-relevant, system to test the potency and selectivity of anti-PAR1 and anti-PAR4 pepducins since platelets possess both PAR1 and PAR4 thrombin receptors with unique Ca2+ signaling profiles (*20*). The PAR1 peptide, P1pal12, was found to completely block PAR1 signaling. Platelet Ca2+ measurements were performed as in Example 1. Platelets were pre-treated with 3 ?M P1pal-12 (open arrow-head) or P4pal-15 (Pal-HTLAASGRRYGHALR (SEQ ID NO:9); closed arrow-head), and then stimulated with 3 Micromolar SFLLRN (SEQ ID NO:24) or 200 Micromolar AYPGKF (SEQ ID NO:27) as indicated. As shown in FIG. 4A-C, 3 micromolar P1pal-12 effectively inhibits PAR1 activation of human platelets by SFLLRN (SEQ ID NO:24), but does not block PAR4 activation by AYPGKF (SEQ ID NO:27) (FIG. 4A). Moreover, a pepducin corresponding to the full-length i3 loop of PAR4, P4pal-15, had no agonist activity but was able to fully antagonize PAR4 signaling.--

B7

On page 49, please replace the paragraph beginning at line 13 with the following:

-- Platelets were then preincubated with either 3 Micromolar P1pal-12 or 3 Micromolar P4pal-15 for 1 min and then challenged with 3 Micromolar SFLLRN (SEQ ID NO:24) or 200 Micromolar AYPGKF (SEQ ID NO:27) and platelet aggregation monitored as in FIG. 1D. Full platelet aggregation traces are also shown for the same amounts of SFLLRN (SEQ ID NO:24) or AYPGKF (SEQ ID NO:27) in the absence (-) of inhibitors. Platelets were pre-treated for 1 min with 0.01-5 Micromolar P1pal-12 or P4pal-15 and challenged with 3 Micromolar SFLLRN (SEQ ID NO:24) or 200 Micromolar AYPGKF (SEQ ID NO:27), respectively. As shown in FIG. 4A, 3 micromolar P4pal-15 blocked AYPGKF (SEQ ID NO:27) activation of PAR4 without affecting SFLLRN (SEQ ID NO:24) activation of PAR1 and is an effective inhibitor of platelet aggregation (FIG. 4B, C). Thus, P4pal-15 is the first described high-potency anti-PAR4 compound (IC50 = 0.6 micromolar in platelets) and is currently being used to help delineate the role of PAR4 in the vascular biology of mice (Covic, Misra, Kuliopulos, (unpublished data).).--

B8

On page 51, please replace the paragraph beginning at line 17 with the following:

-- As an example, using NMR structural analysis, we have identified a region on the extracellular surface of PAR1 which forms part of the ligand binding site for PAR1. This region is comprised of receptor residues P85AFIS89 and is termed ligand binding site-1 (LBS-1). Mutation of this region on PAR1 results in severe defects in receptor activation by intermolecular ligand (i.e. SFLLRN (SEQ ID NO:24)) or thrombin. Addition of lipid-tethered peptides that mimic the receptor ligand binding site(s) might be expected to interfere with thrombin-activated receptor (intramolecular ligand) or exogenously added intermolecular ligand (FIG. 8). Other extracellular loops of the receptor also likely make contact with the ligand and could contribute regions termed ligand binding site-2 (LBS-2), LBS-3, etc.--

B9

On page 51, please replace the paragraph beginning at line 26 with the following:

-- A receptor peptide (LBS1: PAFISEDASGYL-C) (SEQ ID NO:28) was synthesized that contains the P85AFIS89 sequence of PAR1 and adjacent C-terminal residues D90ASGTL95-C that are expected to come into close proximity with the lipid bilayer in the intact receptor (FIG. 9B). The non-lipidated LBS1 peptide was a relatively poor antagonist against thrombin and SFLLRN (SEQ ID NO:24) activation of PAR1-dependent platelet Ca++ fluxes (FIG. 9C, and 9D, respectively). Likewise, the non-lipidated LBS1 peptide did not inhibit 3 nM thrombin aggregation of the platelets (FIG. 9E). In marked contrast, the C-terminally lipidated peptide, LBS1-PE (FIG. 9A) was an effective inhibitor of platelet aggregation. As shown in FIG. 9E, 25 micromolar LBS1-PE completely inhibited 3 nM thrombin-induced platelet aggregation.--

B10

On page 53, please replace the paragraph beginning at line 2 with the following:

-- Activation of the MC4 receptor (MC4R) by melanocortin agonists, such as melanocyte stimulating hormone (alpha-MSH) causes anorexia (loss of appetite) and weight loss in mice. Mutations of the MC4R have been found in extremely obese humans. Here, we synthesized a pepducin, MC4pal-14 (Pal-TGAIRQGANMKGAI) (SEQ ID NO:29) that corresponds to the third intracellular loop of the human MC4R, and tested the pepducin for agonist activity with its cognate receptor. Addition of MC4pal-14 to COS7 fibroblasts transiently transfected with MC4R stimulated adenylate cyclase activity by 35% relative to authentic agonist, alpha-MSH. The activity profile of MC4pal-14 is biphasic with an activating phase (EC_{50}~150 nM) and inhibitory phase (IC_{50}~10 micromolar). These data demonstrate that the pepducins can activate G_S-coupled receptor pathways and that MC4pal-14 and its derivatives may have utility as anti-obesity agents in humans. Further, it is noteworthy that unlike systemically injected peptide agonists like alpha-MSH, these cell penetrating pepducins would be expected to cross the blood-brain barrier to activate receptors such as MC4 located in the central nervous system. (FIG. 7).--

B11

Insert the enclosed sequence listing pages 1-9 at the end of the specification.